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Development of Novel Organic Catalysts for Efficient Chemical Transformations

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Abstract- ***As catalysts promote many useful chemical transformations, catalysis serves as one of the most foundational concepts in contemporary organic synthesis; enhanced reaction rates, improved selectivities, reduced reaction conditions, and an ability to synthesize complicated molecules needed in pharmaceuticals, fine chemical production, materials chemistry, and environmentally sustainable industry manufacturing, these benefits stem directly from catalysis- among rapidly developing new technologies in catalysis, organocatalysis, which offers the advantages of metal-free organic catalysis and uses an assortment of small organic molecules in catalysis, for example, by the utilization of hydrogen bond, covalent interaction, Lewis acid/base interaction, enamine interaction and iminium interaction between reacting molecules and the organocatalysts as activator; in recent years, a variety of organic catalysts, namely amino acid derived catalysts including proline and its derivatives, chiral phosphoric acids, NHCs, thiourea based organocatalysts, peptide based organocatalysts have shown great potential in asymmetric synthesis, carbon-carbon bond construction, oxidation-reduction catalysis and construction of complicated molecule skeletons(Dalko & Moisan, 2004); conventional chemical reactions often depend on precious and scarce metal catalysts and some of them face the problems such as potential metal poisoning of drugs and organic products, potential environmental toxicity caused by precious and difficult-to-recover metal catalysts, narrow substrate applicability and other issues that create demand for efficient, selective and environmental-friendly organocatalytic systems; accordingly, in the present work, a blueprint has been devised for the rationally designed molecular structure of organocatalysts, modification strategy, calculation-based catalyst optimization, mechanistic study and integration of the concept of green chemistry; molecular modeling and theory analysis are regarded as fundamental methods to explore the catalysts; meanwhile some environmental aspects of organic catalysis (reduction in solvent use, energy saving reaction, re-usable catalysis system, atom economy) are also discussed to guide its application in sustainable chemical processes; it is expected that this conceptual work has successfully provided design principle for efficient organocatalytic system in order to enhance reaction control ability, product selectivity and environmental sustainability of organic transformation and to extend its applications of catalytic field more broadly so that organocatalysis can play a more and more important role in the sustainable chemical reactions of future.***

Keywords: Organocatalysis, Organic catalysts, Green chemistry, Asymmetric synthesis, Sustainable chemistry, Metal-free catalysis, Reaction efficiency

I. INTRODUCTION AND BACKGROUND RELATED TO THE STUDY

Modern synthetic chemistry depends highly on organic catalysts, that provide easy ways to improve chemical reactions by activating reactant molecules. Organocatalysis can be seen as catalytic process conducted by organic catalysts. Organic catalysts are generally described as small organic molecules that facilitate a given chemical reaction without being used up themselves, and they can provide a starting material to desired products by transient activated intermediates. While metal-catalyzed processes involve the transition metal activation, organocatalytic processes are based on different activating schemes such as hydrogen bonding, covalent interactions, Lewis acid-base activation, electrostatic interactions and reactive intermediates such as enamine and iminium ion systems and offer efficient control on reaction rates, regioselectivity, stereoselectivity and formation of final product (Dalko & Moisan, 2004). Concept of organocatalysis is similar to enzymatic, in biological processes large organic molecules (e.g. Proteins and cofactors) activate reactions using specially designed active sites for reactant recognition and selective activation that resulted in design of small synthetic molecules to Mimic the most important catalytic features and make it stable, accessible and tunable. Some organic molecules like cinchona alkaloids and amino acids were used historically in

reactions but in systematic method application as a sub discipline started when small molecules like proline derivatives efficiently catalyze asymmetric C-C bond forming reactions (specifically Aldol reactions) with stereochemical control (List, 2007). This breakthrough represented small molecules, and later organocatalysts like secondary amines, phosphoric acids, N-heterocyclic carbenes, thiourea derivatives and peptide catalysts were found out to have performance in tuning all aspects for such catalytic methods when toxic and expensive transition metals could no longer fulfill demands, modern organocatalysis developed since then have found application for wide range of synthesis strategies, including highly selective asymmetric carbon-carbon bonds constructions, fine chemicals, natural products, drug substances, polymers, and advanced materials etc (MacMillan, 2008). Now with improvement on understanding mechanism, computation, catalyst design for each type of catalysts increased their catalytic performances and made it possible to design efficient and specific organic catalysts for required synthesis applications. So organocatalysis changed from a new research discipline inspired from nature and enzymes to an independent chemical science and engineering discipline by integration on molecular design and reaction engineering with green chemistry principles.

II. HISTORICAL DEVELOPMENT OF ORGANOCATALYSIS

Historically the development of organocatalysis can be viewed as a successful evolution in the realm of organic chemistry from a description of reactions influenced by an organic molecule to a catalytic practice capable of efficient and stereoselective control over a variety of reactions; some of the first examples of organic asymmetric catalysts recognized were naturally occurring cinchona alkaloids; these compounds confirmed that a chiral organic molecule could effectively manipulate a reaction and stereo selectively construct a products. The formation of cyanohydrins and their analogs were stereoselective by these agents indicating that small organic molecules could be used effectively as replacement of metal catalysts (Dalko & Moisan 2004). After these examples proline catalyzed reactions were developed for the aldol condensation which formed carbon-carbon bonds via enamine intermediates and still maintained excellent stereochemical integrity and confirmed one key component of asymmetric organic catalysis is using organic compounds as catalytically active species (List 2007). Organocatalysis truly exploded by the 1990's and early 2000s as varied and distinct classes of catalytic organic molecules were discovered. These include secondary amines, chiral phosphoric acids, hydrogen bonding catalysis, chiral thioureas and most importantly in this context N-heterocyclic carbenes. These groups are active through many different activation patterns but the significance of NHCs comes from these carbenes serving as good Lewis bases, acting through their nucleophilic nature to create reactive intermediates, like the Breslow intermediate, driving a variety of reactions. Such as benzoin condension, acylation and C-C bond-forming events (Enders et al. 2007). The success with asymmetric catalysis allows complex chiral organic molecules to be synthesized efficiently and with stereoselectivity in a safe and green fashion which is especially useful in fine chemical synthesis or in preparation for drug discovery efforts. Most recently the development of photoredox organocatalysis demonstrates that traditional metal photocatalysts can be replaced through visible light mediated activation allowing chemists to access a new frontier of reactions using organic catalysts (Prier et al. 2013). Organocatalysis has become a powerhouse field in modern organic synthesis, the development of which shows it is highly effective in many different cases, the impact of which could be seen with the bestowal of the novel prize in chemistry to asymmetric organocatalysis

III. IMPORTANCE OF ORGANIC CATALYSTS IN CHEMICAL TRANSFORMATIONS

Recent growth has focused on organic catalysts due to the efficient, selective and greener alternatives they can offer for traditional catalytic systems, especially transition-metal based catalysts and their role in utilizing non-metallic activation can be greatly seen as furthering the application of organic catalysis as a tool for sustainable chemical synthesis; environmental benefits provided by organocatalytic reactions can be significant because metal free organocatalytic reaction systems would diminish any questions regarding metal toxicity and metal residue, soil contamination and

disposal of metal wastes (Dalko & Moisan, 2004); furthermore organocatalysts are generally characterized by relatively moderate reaction conditions with typically milder temperatures and pressures and energy reduction which can in a way relate to lower impact on environment and a higher efficiency of process; Synthetic organic catalysts have demonstrated great advantages regarding efficiency on the chemi-, regio- and stereoselectivity that is obtained through directing reaction course, via hydrogen bond activation, covalent activation, enamine formation, iminium activation and stabilization of transition state(List, 2007); Functional group tolerancy offered by organic catalyst system also makes a valuable aspect through transforming a broad range of molecules without many protecting group strategies involved, thus increasing the synthetic variability and shortening necessary reaction steps; Moreover industrial scale applications can be readily seen, specifically in fine chemical and pharmaceutical manufacturing processes where organocatalysts can promote synthesis of both medicinally active products and valuable specialty materials, also leading to high efficiency and less complex purifications; organocatalysis may particularly appeal for pharma industry due to high purity of the product and avoidance of metal catalyst residues as a benefit (List, 2007); in conclusion, development of potent organocatalysts should be regarded as an innovation to attain greener, selective and economically attractive reactions by combining green chemistry principles, structure-based catalyst designs, real industrial demands so as to further enrich catalysis knowledge as to advance future chemical synthesis.

IV. RESEARCH PROBLEM

Recent breakthroughs in catalytic technologies, especially the enabling power and specificity for efficient organic transformations, nevertheless the current catalytic systems are still suffering from a number of serious issues that constrain the expansion of their application to sustainable and large-scale processes; Many transition-metal catalysts such as those involving the use of precious and rare elements, (such as Pd, Pt, Rh and Ir), have displayed unprecedented activities and selectivities for many transformations, their high economic cost is always an issue that restricts the widespread development and the supply of such metal sources is becoming limited that raise concerns over sustainable economic development and resource availability; moreover, a major concern regarding to potential toxicity, persistence in the environments, as well as contaminating the final product with residual metals that are strictly regulated as impurity level in the pharmaceutical field are all challenging that commonly need tedious purification procedures which would increase operational costs and waste produced (Hartwig, 2010); On the other hand, organic catalysts provides green and readily available alternatives to transition-metal catalysts, however, they also meet limitations such as poor activity for some transformations that often demand relatively higher loadings than their metal counter parts, poor recyclability and limited substrate scope (MacMillan, 2008); Besides, some of the organocatalysts systems often still require specific experimental conditions, such as, special solvent and reaction temperatures and often complex experimental procedure for the catalyst synthesis and operation; Accordingly, one of the main focuses in the area of modern organic synthesis focuses on the rationally designing new catalyst architectures with controlled molecular designs, defined active-site structures and organizations, to impart higher catalytic performance (catalytic efficiency), good stability and broad substrate scope that to realize efficient and environmentally benign transformations; Advanced strategies such as guided molecular design through computer assistance, exploration of reaction mechanisms, systematic investigation and rational improvement of catalytic systems using green chemistry principles must be considered in order to develop high efficient catalysts, especially for the future; Thus, design of second generation organic catalysts should endeavor to reach optimum performance in catalysis and environmentally friendly aspect as well as economic feasible for industrial applications in pharmaceuticals, fine chemistry and so on.

V. GREEN ORGANIC CATALYSIS

The field of green organocatalysis is an important facet of sustainable synthetic chemistry that endeavors to merge catalysis with green chemistry principles. These methods focus on the formulation of chemical transformations and processes with reduced impact on

the environment, the efficient accomplishment of desired chemical outcomes and selectivity. By applying organocatalytic systems to reactions, important green chemistry aspects including the enhancement of atom economy, less waste generation and higher energy efficiency could be attained in organic chemical reactions, allowing the construction of bond-forming processes without excess reactants, unwanted products formation and less loss of reactant atoms as (Anastas & Warner, 1998), thus making atom economy vital because catalytic reactions can be effectively designed with the input atoms channeled into the target products thus lowering the consumption of materials and improving the sustainability of the synthesis processes. This also helps reduce environmental waste from complicated isolation processes, solvent usage, and chemical disposal. Besides this, the majority of the reactions utilizing organic catalysts can be achieved under mild condition such as room temperature and at ambient pressure which consequently allows higher energy efficiency as compare to conventional processes at high temperature and pressure (Sheldon, 2017). Other important aspects of green organocatalysis involve new techniques of reaction which are solvent-free reactions and this technique is a greener option than volatile organic compounds, simplifying the process of extraction of the product, so catalytic systems using water as reaction media were also developed. Water is an inexpensive solvent and does not poison catalyst or organic reactants as it possesses great advantages from environmental standpoints and are usually much safer, cheaper and non-toxic as compared to conventional organic solvents. Recyclable organocatalysts and supported organocatalytic systems are areas of much interest for recovery and reuse of organic catalysts. By providing sustainable economic and industrial processes, one-pot reaction has emerged as a promising green technique where many sequential synthetic steps are collapsed in one reaction pot that limits waste production and consumption of solvents and reagents, reduces reaction time and simplifies separation procedure. As a result, through smart molecular design and design of reaction engineering to construct environmentally friendly organic catalysts, we would get efficient cleaner synthesis of fine chemicals, pharmaceuticals and advanced materials and a deeper understanding towards organocatalysis as a green chemical technology can be achieve that will pave way for sustainable technology that can provide further development for green chemistry and industrial transformation.

VI. RESEARCH METHODOLOGY

The envisioned conceptual research paradigm for novel organic catalyst development is presented which proceeds with rational catalyst design according to certain fundamental requirements such as high catalytic activity, and excellent chemo-, regio-and stereoselectivity. Other requirements for catalyst development are good chemical and thermal stability, low toxicity and environmental friendliness and feasibility of synthesis, where molecular structure designs should accommodate suitable site and space for efficient substrate activation and guided reaction pathways. A catalyst development work flow is schematically designed to be a multistep one, starting from catalyst concept, molecular modification, and computation prediction and continuing up to catalyst synthesis, characterization and reaction studies, thus demonstrating a clear correlation between the structure of catalysts and their intrinsic reactivity as performance. Thus, all aspects will take into account of relevant parameters such as Macmillan (2008). In catalyst concept part, active groups in specific positions, appropriate binding mode, required steric and electronic environments are integrated with each other into an active molecule scaffold by activating or transforming target substrate through hydrogen bonding, covalent activation, and Lewis's acids/bases addition or intermediates addition. To improve a catalyst activity, selectivity, and compatibility to the substrate as well as enhance its solubility and stability, we must conduct molecular modifications by precise control of the catalyst structure. Before being practically synthesized and studied, the catalytic activities, product yields and selectivity as well as catalytic system parameters could be evaluated using computational approaches. Computational calculation (including molecular modelling and quantum chemical calculation) is suggested to explore complex of catalyst and substrates, transition states, and reaction mechanism so as to predict the potential performance before preparation of target catalysts and hence avoid uneffecient research. These can thus result in rapid discovery. (Tropsha, 2010). At last, promising catalysts candidates are finally to be

systematically synthesized using well-established synthetic methods, and then characterized by modern spectroscopical and chemical techniques to ensure their chemical structures and purity. And subsequent catalytic tests of reaction conversion, product yields, stereoselectivity as well as activity(loading of catalysts and TON/TOF) in addition to substrate scope will be performed, then optimum conditions such as temperature, pressure, solvents, reaction times, and concentrations should be optimized to give satisfactory catalytic performance and sustainable chemical environment, while iterative process should involve repeated step from structural tuning of the catalyst until obtain the promising catalyst, and optimize reaction parameters and working process of such novel catalysts to accomplish efficient, selective and green reactions.

VII. COMPUTATIONAL CATALYST DESIGN

A key method in modern synthetic chemistry involves the design of computational catalysts: computational techniques are enabling researchers to use predictive models to study the behavior of catalysts and optimize molecular structures. Moreover, a better prediction capability could decrease both the time and the resources needed to optimize catalytic molecules in experimental procedures. To assist with this design methodology that allows for rational approaches in a search for good organic catalysts, techniques used for the modeling of molecules include studying various structural aspects such as catalyst geometry and electronic properties, substrate interactions with a catalyst, and plausible catalytic mechanisms prior to a synthetic stage and laboratory execution. In studying a catalytic species, computation would aim to predict catalyst structures based on analysis of various molecular properties like conformational aspects, steric interactions of substituents, hydrogen bonding effects or electronic features influencing the mechanism, as well as identify suitable reaction pathways, taking in to account all intermediates formed and stabilized transition states, and potential other, undesired reactions (Cramer, 2004). Computation using Density Functional Theory (DFT) has been utilized in studies pertaining to catalysts as one of the dominant computing techniques because it provides details related to molecules electronic structure, energetics of reactions as well as their mechanisms, based on computation of values pertaining to transition states, activated molecules, intermediate species and a reaction path (or coordinate) (Parr & Yang, 1989). When utilized to perform a DFT calculation in a study relating to organocatalysts, information relating to activation of molecules, transition states, unstable intermediates and reaction mechanisms are obtained. The DFT method is also employed to determine preferred pathways among alternative ones or to elucidate controlling factors related to activity and selectivity. Its applications also involve understanding and predicting influence of certain factors over catalytic action and consequently in synthesis of improved catalytic models. Specifically, in organocatalysis, computation could provide better understanding and ability to explain subtle aspects of catalysis, such as mechanisms operating in hydrogen-bonding-mediated catalyses, or enamine/iminium chemistry where the stereochemistry in the activated molecules is crucial. They are also useful in searching for promising catalyst candidates and in determining specific substituent requirements for such models; in addition, such methodology is well-suited in predicting effective and ecologically favorable models of catalysts by reducing reliance on experiments in testing new models. Integrated approach involving molecular modelling and DFT calculation can provide new pathways in developing effective and selective organic catalysts and efficient organic reactions.

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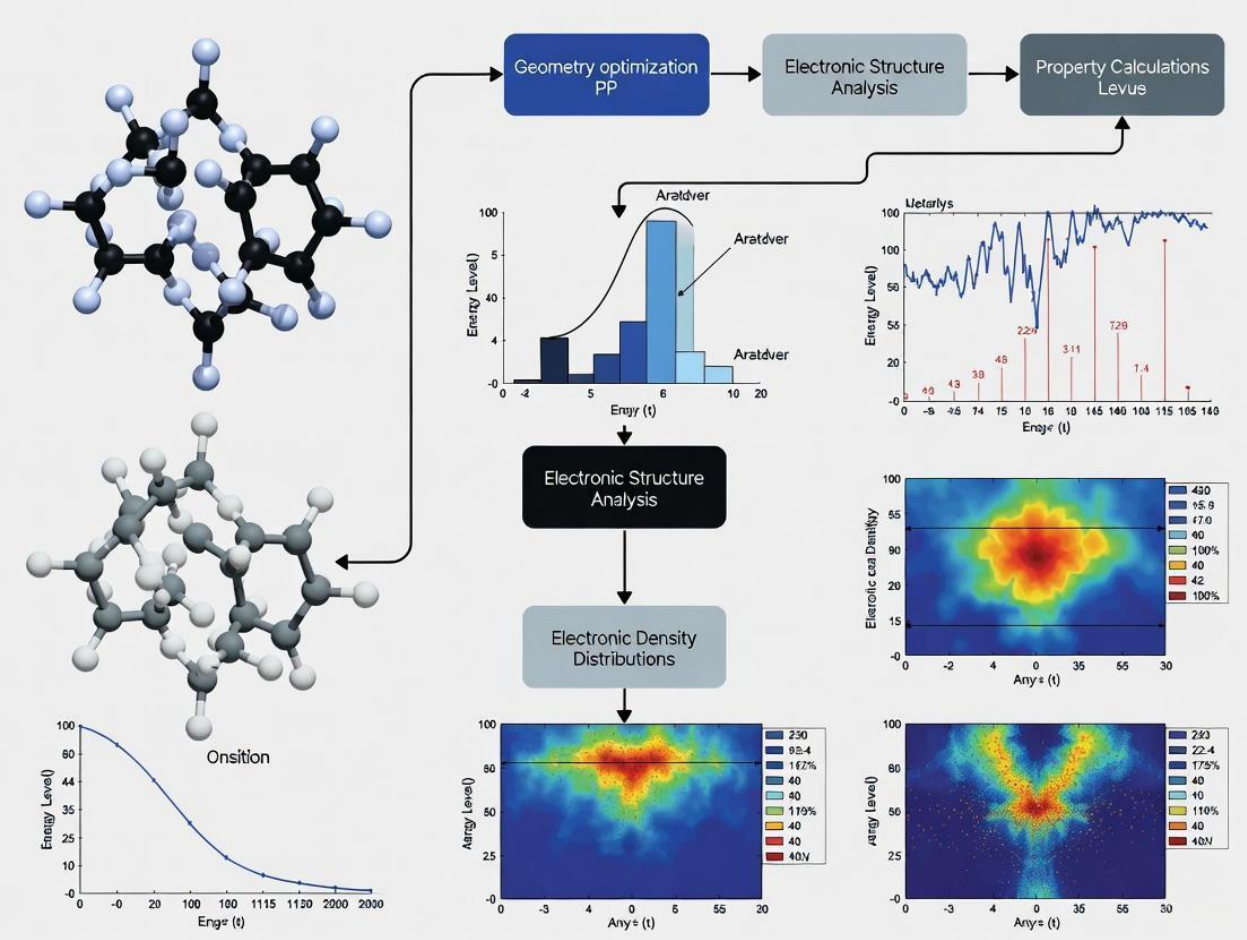

Above image showing Computational Catalyst Design related to Development of Novel Organic Catalysts for Efficient Chemical Transformations

Catalytic Performance Evaluation

Catalyst evaluation is essential in the study of new organic catalysts since it gives us insights into efficiency, selectivity, stability and practicability of the catalyst in chemical transformations; the reaction efficiency (RE) is determined by examining variables such as percentage of conversion and percentage of yield, which represent the percentage of substrate consumed by the catalytic system or product obtained respectively and may be used to compare activities under different circumstances (Dalko & Moisan, 2004); high catalysts efficiency means increased efficiency in substrate activation and optimal pathway, shorter reaction times and/or smaller catalyst loadings, which may affect sustainability of a synthetic process. The evaluation of selectivity is critical as the efficiency in discriminating between desired and unwanted products may distinguish a successful catalyst from one that is merely effective; catalyst selectivity has to be evaluated by considering chemical selectivity, regioselectivity and stereoselectivity or enantioselectivity; chemical selectivity determines the preferential reactions between different functional groups in the presence of several possibilities; regioselective catalysts promote formation of specific regioisomers, and enantioselective catalysts, chiral ones, develop a tendency in synthesizing certain enantioisomers; especially stereoselective reactions play an important role in pharmaceutical synthesis, due to the specific biological responses triggered by each enantiomer (List, 2007); catalyst stability is important for its use in processes over time, and can be verified by analyzing recycling behavior and calculating turnover number (TON) or frequency (TOF); repeated recycling indicates an able catalyst over multiple steps and TON,TOF indicates the number of turnovers achievable per catalyst molecule

throughout its useful life and per time unit respectively.

VIII. DISCUSSION

With the conceptual construction of new organic catalysts and careful observation to reaction mechanisms the efficiency of chemical reactions will improve because the catalyst helps controlling reaction path, active the substrate, and forms product through rational modification of molecules and clear understanding to reaction mechanism, catalysts modification including tuning catalysts functional group, surrounding steric environment, electronics distribution, or their active sites will lead to increase its efficiency to react faster, provide selectivity and improve applicability to more subjects with less loading of catalysts, as well as to explain their active mechanism on making transition-state more stable (MacMillan, 2008); on studying active mechanism, information of intermediate production and controlling reaction result is obtain, this will lead to set up clear relationship between structure of catalysts and their effects on activating substrate and select producing product, the better understanding on mechanism guides scientists build up new catalytic active site with desired property for a definite reaction; in the terms of green chemistry, organic catalysts would benefit in this field. Metal-free reaction with benefit of not involving metal in catalyst synthesis or reaction, without concerning toxicity and environmental affect by metal, and lowering the potential pollution in the meantime, producing waste with less number because the mechanism of catalyst can greatly control products outcome. So, it will improve reaction conditions toward mild ones, saving energy consumption; what's more, mild condition would accommodate more of environmentally benign synthetic pathways. Catalyst architecture and catalytic efficiency have been accepted the most crucial relations to establish in terms of catalyst activity and it can decide the way substrate binds to catalysts, stabilize the transition states and direct path selectivity; integrating molecular engineering with computational analyze, mechanistic studies and green chemistry may speed up the next generation organic catalysts and broaden their application range for medicine synthesis, fine chemical manufacturing and so on.

IX. FUTURE PERSPECTIVES

In the future, design of organic catalysts will be driven by cutting-edge technologies, sustainability strategies, etc. This will involve combination of computation, artificial intelligence, environmentally benign synthetic approach for catalyst discovery and enhanced reaction performance and AI assisted catalyst design are of paramount importance and will play a vital role by performing a predictive examination to identify effective catalysts, study behavior of reaction, analyze interaction of molecules prior to experimental study to select appropriate catalyst. Chemical data bases would also lead to a predictable assessment to assess the outcome of reaction with use of machine learning techniques that would help in identification of influential descriptors of molecules and screening of catalyst candidates quickly to provide the desired yield and selectivity (Gomez-Bombarelli et al., 2018). Sustainable chemistry in the field of organocatalysis is predicted to grow in scope through the utilization of renewable feed stock, strategies toward biomass conversion and absence of solvents in synthetic procedures which will help reduce use of petrol based resources, minimizing generation of waste by implementation of the 12 green chemistry principles. Use of photoredox catalysis, i.e., visible-light induced photoredox catalysis offers promising possibilities with use of light as the energy source and environmentally benign chemical transformation for reaction by formation of radical intermediates under mild reaction conditions, without utilization of hazardous traditional energy consumptive approaches (Prier et al., 2013). Recovery and reusing organic catalyst and subsequent integration into circular chemistry is an additional goal that is expected with regard to the development of recyclable organic catalysts by enhancing efficiency through re-use and minimizing generation of waste from the material and to promote synthesis. Computation aided catalyst design together with mechanistic understanding of reaction processes, use of green chemistry, and innovative reaction engineering will lead to design of efficient, selective and sustainable catalysts. Integration of AI, machine learning approaches, green catalysis and photocatalysis will pave the way for developing organic catalysis for efficient, industrially relevant and environmentally benign future chemical synthesis.

X. CONCLUSION

Organic catalysts are proved to be excellent and environmentally benign alternative over conventional metal mediated catalytic system in many respects as it allows efficiently perform chemical transformations based on various activation modes, eliminating the problem of metal toxicity, pollution to the environment and complicate purification of products. Development of organocatalytic approach considerably widened chemical transformations possible, and gave access to selective and milder ways in synthesizing molecules of pharmaceutical, fine chemical, and materials interest. Rationally designing catalysts by manipulation of their molecular architectures, electronics, sterics, and mechanisms became a key strategy to achieve higher activity and selectivity and to realize the targeted molecules and reaction control, especially when aiming to tune their reactivity, compatibility of substrate, stereoselectivity control. In-silico methods like modeling and theoretical calculation have been exploited as predictive tools to understand catalyst behaviors and guide structural optimization and reaction mechanism exploration. Merging synthesis, computation based catalytic design, mechanical study, and green chemistry concepts is crucial in establishing new catalytic systems which may play a significant role in upcoming technological advancement. Thus, continuous development of organocatalytic systems will play an essential role in the future of chemistry manufacturing through the development of processes that enable to achieve high selectivity with high energy economy in an eco-friendly and user-friendly manner.

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